

in medical schools nationwide. Obviously, over this period and earlier, our department has been well served by nationally and internationally recognized basic scientists.

I do not intend or attempt to refute the assumptions of the owners of the digits from which the thumbnails were extracted, but, as we all have experienced in attempting to reduce the unnecessary and unwarranted harm inflicted by ill-manicured nails of infants or head-strong pets, the process often entails excessive and useless loss of energy. Useless energy expenditure notwithstanding, the data I present are correct and can be substantiated by the public record. I would have expected an august publication such as *CMAJ* to assess the veracity of the spoken word before it was immortalized in print.

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[Dr. T. Alexander McPherson, president of the Canadian Medical Association, replies:]

The special report, with comments by Douglas Waugh, past executive director of the Association of Canadian Medical Colleges (ACMC), should be required reading for all interested in medicine and medical education in Canada.

The report contains information of interest to us all. For instance, might not an applicant to medical school find the information about who stands the best chance of getting into a Canadian medical school useful? Do you not agree with Martin Hollenberg, dean of medicine at the University of Western Ontario, that students are not being sufficiently exposed to health care planning? I know that our provincial health ministers would. Did you know that the estimated cost for producing a medical doctor in Canada is probably as high as \$100 000, and don't you agree, as J. Donald Hatcher, dean of medicine at Dalhousie University, suggests in the report, that the different costs in different provinces are probably due to underfunding of some medical

schools as compared with others? Will residents, interns and deans of postgraduate training not be interested to find out what some of our schools do to provide counselling on postgraduate training, career choices and licensing requirements? Surely all of us, including ministers of health, are interested in the study of medical manpower mobility done by the ACMC and the estimate that nearly one in five graduates from English-Canadian medical schools will have left Canada to practise elsewhere — mainly in the United States — by about 15 years following graduation. Finally, is the registry of organizations involved in medical education from the undergraduate level not helpful? And is the fact that the Canadian Federation of Medical Students has no address, only a telephone number, telling us something about the future?

As for the "thumbnail sketches" of our 16 medical schools, they are just that — distillations of comment from some of the most senior and knowledgeable academics in this country as recorded and reported by Charlotte Gray. They are not, and do not purport to be, the equivalent of the CACMS-LCME accreditation. They are, however, a view from the "inner outside" of our schools. Perhaps, rather than express outraged indignation, we should reflect on the criticisms and consider solutions to the problems noted — if, indeed, they exist.

I say Well done, Charlotte Gray. In my opinion her kind of commentary, and that of Dr. Waugh, is part of the reason *CMAJ* fares very well in comparative readership studies and last year was cited in the international medical literature more than 3000 times.

T. Alexander McPherson, MD
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Adverse effects of NSAIDs on renal function

Linton's timely and important paper on the adverse effects of non-steroidal anti-inflammatory drugs

(NSAIDs) on renal function (*Can Med Assoc J* 1984; 131: 189-191) prompts me to report the following case, which suggests an additional renal problem related to NSAID use.

Case report

The patient, a married woman, was born in eastern Europe in 1923 and came to Canada as a young woman. Most readers are aware that tuberculosis was very common in parts of Europe until the end of World War II, and a high percentage of the population were considered to have had primary infection.

In May 1971 the patient was investigated for recurrent urinary tract infection, and intravenous pyelography showed two calcified cysts in the left kidney due to some deformity of the calices. There appeared to be some mottled calcification centrally within one of the cysts. An opacity in the right side of the abdomen had the appearance of a calcified lymph node. There had been no change in the spine since the previous examinations, in 1967 and 1968. In a patient of this age and ethnic background such findings are likely indicative of old, healed tuberculosis.

According to the records of her family physician the patient first received phenylbutazone in 1958 for back pain. The medication prescribed was Buffazone, a buffered preparation containing 100 mg of phenylbutazone. The drug was again prescribed in 1965, 1967 and 1972 and on two occasions in 1973. While the records do not reveal in all cases the dosage or duration of administration, on a number of occasions the dosage was one tablet four times a day for 30 days.

In May 1975 the patient presented with frequency, urgency, burning and recurrent cystitis. She was again seen in September and October of the same year complaining of urinary symptoms and hematuria, and finally in December of that year a diagnosis of genitourinary tuberculosis and a nonfunctioning left kidney was established. Acid-fast bacilli were cultured from the urine. A decision to perform a left nephrectomy was later reversed, and following lengthy treatment the patient eventually recovered.



FIRST EFFECTIVE TREATMENT OF PERIPHERAL VASCULAR DISORDERS OF THE EXTREMITIES

Pharmacological Classification Vasoactive agent

Actions

Trental (pentoxifylline) is a xanthine derivative. It belongs to a group of vasoactive drugs which improve peripheral blood flow and thus enhance peripheral tissue oxygenation. The mechanism by which Trental achieves this effect has not been determined, but it is likely that the following factors are involved:

1. Trental, as other xanthine derivatives, relaxes certain smooth muscles including those of the peripheral vessels, thus causing vasodilation or preventing spasm. This action, however, may have a limited role in patients with chronic obstructive arterial disease when peripheral vessels are already maximally dilated.

2. Trental improves flexibility of red blood cells. This increase in the flexibility of red blood cells probably contributes to the improvement of the ability of blood to flow through peripheral vessels (hemorheologic action). This property was seen during *in vitro* and *in vivo* experiments with Trental but the correlation between it and the clinical improvement of patients with peripheral vascular diseases has not been determined.

3. Trental promotes platelet deaggregation.

Improvement of red blood cell flexibility and platelet deaggregation contribute to the decrease in blood viscosity.

Pentoxifylline is almost completely absorbed after oral administration. Trental 400 mg sustained-release tablet showed an initial peak plasma pentoxifylline concentration 2 to 3 hours post-administration. The drug is extensively metabolized. Biotransformation products are almost exclusively eliminated by the kidneys.

Food intake before the administration of Trental delayed the absorption but did not decrease it.

Indications

Trental is indicated for the symptomatic treatment of patients with chronic occlusive peripheral vascular disorders of the extremities. In such patients Trental may give relief of signs and symptoms of impaired blood flow, such as intermittent claudication or trophic ulcers.

Contraindications

The use of Trental (pentoxifylline) is contraindicated in patients with acute myocardial infarction, patients with severe coronary artery disease when, in the physician's judgement, myocardial stimulation might prove harmful, patients with hemorrhage, patients who have previously exhibited intolerance to pentoxifylline or other xanthines such as caffeine, theophylline and theobromine, patients with peptic ulcers or recent history thereof.

Warnings

Since Trental (pentoxifylline) is extensively metabolized in the liver and eliminated through the kidneys, the use of this drug is not recommended in patients with marked impairment of kidney or liver functions. Patients with less severe impairment of these organs should be closely monitored during Trental therapy and they may require lower doses.

Pediatric use: The use of Trental in patients below the age of 18 is not recommended as safety and effectiveness has not been established in this age group.

Precautions

Caution should be exercised when administering Trental (pentoxifylline) to patients with low or labile blood pressure. In such patients any dose increase should be done gradually.

Trental should be used with caution in elderly patients as peak plasma levels of pentoxifylline and its metabolites are moderately higher in this age group. Elderly patients had a slight increase in the incidence of some adverse effects. Careful dose adjustment is therefore recommended. Use in pregnancy and in nursing mothers: Reproduction studies have been performed in rats, mice and rabbits at doses up to 23, 2 and 11 times the maximum recommended daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to pentoxifylline. The drug has been shown to cross the blood-placenta barrier in mice. There are no adequate, well-controlled studies in pregnant women.

Therefore, Trental is not recommended for women who are, or may become, pregnant unless the expected benefits for the mother outweigh the potential risk to the fetus. The use of Trental in nursing mothers is not recommended as its safety under this condition has not been established. It is not known if Trental is excreted in breast milk.

Drug Interactions

Trental (pentoxifylline) may potentiate the action of antihypertensive agents. Patients receiving these agents require blood pressure monitoring and possibly a dose reduction of the antihypertensive agents.

Combined use with other xanthines or with sympathomimetics may cause excessive CNS stimulation.

No data are available on the possible interaction of Trental and erythromycin. However concurrent administration of erythromycin and theophylline has resulted in significant elevation of serum theophylline levels with toxic reactions. In patients treated with hypoglycemic agents, a moderate adjustment in the dose of these agents may be required when Trental is prescribed.

Adverse Reactions

The most frequent effect reported with Trental (pentoxifylline) is nausea (14%). Individual signs/symptoms not marked with an asterisk occurred at an incidence below 1% (* = incidence between 1% and 3%).

Cardiovascular system

Flushing*, chest pain, arrhythmia, hypertension, palpitations, shortness of breath.

Central nervous system

Dizziness/lightheadedness (9.4%), headache (4.9%), drowsiness/sleepiness, tremor, agitation, anxiety, confusion, insomnia, restlessness.

Gastrointestinal system

Nausea (14%), vomiting (3.4%), abdominal discomfort*, bloating*, diarrhea*, dyspepsia*, abdominal burning, abdominal pain, anorexia, flatulence, constipation, hemorrhage, heartburn, salivation, dry mouth/throat.

Integumentary system

Rash, sweating.

Organs of special sense

Blurred vision, scotoma, lacrimation.

Miscellaneous

Malaise*, muscle aches/spasms, weight change, anaemia, backache, bad taste in mouth, leg cramps, fever, weakness.

Symptoms and Treatment of Overdosage

The signs of overdosage with Trental include flushing, hemoemesis, absent reflexes, tonic-clonic convulsions, and loss of consciousness.

In addition to gastric lavage, treatment is symptomatic; special attention must be given to supporting respiration, maintaining systemic blood pressure and controlling with intravenous diazepam.

Dosage and Administration

The recommended starting dosage of Trental (pentoxifylline) is 400 mg twice daily after meals. The usual maintenance dose is 400 mg twice or three times daily. A maximum dose of 400 mg three times daily should not be exceeded.

It may take up to two months to obtain full results.

Trental 400 mg tablets must be swallowed whole.

Supply

Trental (pentoxifylline) is available as 400 mg, pink, oblong, sugarcoated, sustained-release tablets, packed in Unit-Pack boxes of 60 blister-packed tablets.

Product Monograph available on request.

Hoechst
Hoechst Canada Inc., Montréal H4R 1R6

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Comments

In light of evidence presented previously of an association between the use of NSAIDs and the reactivation of pulmonary tuberculosis,¹ this case provides reason to suspect that reactivation of renal tuberculosis should now be considered a probable adverse effect of this group of drugs.

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Reference

1. Tomasson HO, Brennan M, Bass MJ: Tuberculosis and nonsteroidal anti-inflammatory drugs. *Can Med Assoc J* 1984; 130: 275-278

Manitoba Medical Association's stand on binding arbitration

The newsbrief on Manitoba in the Sept. 1, 1984 issue of *CMAJ* (131: 465) is fraught with factual inaccuracies with which I must take issue.

Manitoba Health Minister Laurent Desjardins did, in fact, tell the Manitoba Medical Association (MMA) he was going to ban extra-billing but said it would not be immediately. (He has since indicated he will ban it within the next year.) Our February referendum, asking members if they would *exchange* extra-billing for a fair and reasonable form of binding arbitration, was done not "just in case" extra-billing was banned but because it was clear that extra-billing would be banned, and the association required a mechanism for resolving fee disputes in its place.

The referendum did have a 75% response rate, but 75% of those voting said they favoured obtaining binding arbitration *in exchange for the banning of extra-billing*. The question on the referendum made it clear that the two items were linked and that extra-billing (not opting-out) would be given up only if fair and reasonable binding arbitration were offered in its place.

There is no doubt that this mandate is as clear today as it was when the responses were compiled in Feb-